Translation

PCT/EP2003/002328

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 102 09 979.0	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP2003/002328	International filing date (*day/month/year*) 06 March 2003 (06.03.2003)	Priority date (*day/month/year*) 07 March 2002 (07.03.2002)
International Patent Classification (IPC) or national classification and IPC A61K 9/28		
Applicant RATIOPHARM GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 28 August 2003 (28.08.2003)	Date of completion of this report 21 April 2004 (21.04.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP2003/002328

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-19, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages 1-16, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:

pages 1/1, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP 03/02328

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	5, 7-9, 11, 15, 16	YES
	Claims	1-4, 6, 10, 12-14	NO
Inventive step (IS)	Claims		YES
	Claims	1-16	NO
Industrial applicability (IA)	Claims	1-16	YES
	Claims		NO

2. Citations and explanations

Reference is made to the following documents:

D1: US-A-4 871 549 (UEDA YOSHIO ET AL) 3 October 1989 (1989-10-03)

D2: US 2002/022054 A1 (SAKO KAZUHIRO ET AL) 21 February 2002 (2002-02-21)

D3: EP-A-0 612 520 (PFIZER) 31 August 1994 (1994-08-31)

D4: WO 01 68056 A (MERCK PATENT GMBH; KRAUS EDGAR (DE); MATTIS JOCHEN (DE); SCHAEFFLE) 20 September 2001 (2001-09-20)

D5: US-A-5 916 595 (CHOU JOSEPH ET AL) 29 June 1999 (1999-06-29)

D6: EP-A-0 485 840 (ROEHM GMBH) 20 May 1992 (1992-05-20)

Explicit reference is made only to those relevant passages that are not cited in the international search report.

PCT Article 33(2)

The subject matter of claims 1-4, 6, 10 and 12-14 is not novel and therefore does not satisfy the criteria of PCT Article 33(2).

D5 discloses a medicament containing lovastatin. The agent is released in two stages, the first stage lasting approximately two hours from the time at which the medicament was taken and considerably less than 20% of the agent being released within this period of time. From this period of time onwards, the agent is then released at at least twice the speed. A swellable substance (hydroxypropylmethyl cellulose and polyethylene glycol) is deposited between the core and the water-insoluble layer (cellulose acetate). The subject matter of claims 1-4, 6, 10 and 12-14 is therefore not novel over D5.

PCT Article 33(3)

The present application does not meet the requirements of PCT Article 33(3) since the subject matter of claims 1-16 does not appear to be inventive.

D1 appears to represent the closest prior art. D1 discloses a time-controlled explosion-type system having release rates such as are claimed in the present application. The essential difference with respect to the subject matter of the present application consists in the selection of the agent.
The problem of interest can therefore be defined as follows:
Finding a new agent suitable for use in a time-controlled explosion system.
To solve this problem, the present application proposes the use of cholesterol reducers, more specifically HMG-CoA reductase inhibitors and fibrates.
D4 teaches the use of time-controlled explosion systems for the application of agents that are intended to be effective at night (e.g. glucocorticoids for bronchial

asthma). The fact that specifically HMG-CoA reductase inhibitors are most effective during the night, since this is when the circadian maximum of the endogenic cholesterol synthesis occurs, is already well known.

In the light of the teaching of the prior art, the following is noted:

With respect to the subject matter of claims 1-4, 6, 10 and 12-14, the applicant is advised that, even if novelty were able to be established over the aforementioned prior art, the present application does not appear to contain any basis for acknowledging an inventive step for the subject matter of the claims in question.

With respect to the subject matter of claims 5, 7, 8, 9 and 11, the following is noted:
The galenic form described in the claims in question with the corresponding pharmokinetic properties and therapeutic aims is already well known from the prior art. To solve the problem in question, the applicant has selected a group of agents from a list which all contain agents that influence circadian physiological processes. In the selection of specifically this class of agent, it is not apparent where the surprising effect might lie which could lead to the establishment of an inventive step.

With respect to the subject matter of claims 15 and 16, the following is noted:
The present application proposes, as a solution to the problem of interest, the provision of a medicament whose incorporated agent has different speeds of release.
The prior art does not disclose such a product.
The problem of interest does not therefore appear to be solved by the subject matter of claims 15 and 16 and an

inventive step (PCT Article 33(3)) can therefore be acknowledged.

PCT Article 33(4)

The subject matter of claims 1 to 16 is considered industrially applicable (PCT Article 33(4)).